# Early standardized clinical judgement for syncope diagnosis in the emergency department

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Short Title: Clinical judgement and syncope

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**Abstract:**

**Background:** The diagnosis of cardiac syncope remains a challenge in the Emergency Department (ED)

**Objective:** Assessing the diagnostic accuracy of the early standardized clinical judgment (ESCJ) including a standardized syncope-specific case report form (CRF) in comparison to a recommended multivariable diagnostic score.

**Methods:** In a prospective international observational multicenter study, diagnostic accuracy for

cardiac syncope of ESCJ by the ED physician among patients ≥40years presenting with syncope to the ED was directly compared to that of the Evaluation of Guidelines in Syncope Study (EGSYS) diagnostic score. Cardiac syncope was centrally adjudicated independently of the ESCJ or conducted work-up by two ED specialists based on all information available up to 1-year follow-up. Secondary aims included direct comparison with high-sensitivity cardiac troponin I (hs-cTnI) and B-type natriuretic peptide (BNP) concentrations and a Lasso-regression to identify variables contributing most to ESCJ.

**Results:** Cardiac syncope was adjudicated in 252/1494 patients (15.2%). The diagnostic accuracy of ESCJ for cardiac syncope as quantified by the area under the curve (AUC) was 0.87 (95%CI 0.84-0.89), and higher compared to the EGSYS diagnostic score (0.73 (95%-CI 0.70-0.76), hs-cTnI (0.77 (95%-CI 0.73-0.80)) and BNP (0.77 (95%-CI 0.74-0.80), all p<0.001. Both biomarkers (alone or in combination) on top of the ESCJ significantly improved diagnostic accuracy.

**Conclusion:** ESCJ including a standardized syncope-specific CRF has very high diagnostic accuracy and outperforms the EGSYS score, hs-cTnI, and BNP.

**Introduction:**

Syncope is a transient loss of consciousness associated with an inability to maintain postural tone due to global cerebral hypoperfusion[1] and is a symptom commonly reported by patients presenting to the emergency department (ED).[2] Establishing the cause of syncope is essential as the risk of death is substantially higher in patients with a cardiac cause of syncope in comparison to those with vasovagal or orthostatic etiologies.[1,3,4]

Unfortunately, the ability of ED physicians to rapidly identify the underlying cause of syncope is often limited by scant patient recall, absence of witnesses, the paroxysmal nature of cardiac arrhythmias, unstandardized patient assessment, and time pressure.[5] Therefore, the exact syncope etiology remains unclear at ED discharge in about 25-40% of patients.[6] The concern of

possible cardiac syncpe leads to high admission rates and numerous cardiac investigations.[7] Approximately 50% of patients who present to the ED with syncope are admitted,[1] and around one third of these admission are considered inappropriate and possibly even harmful.[8–11]

High hospitalization rates for patients with syncope may at least in part be related to less standardized patient assessments as compared to other common presenting symptoms such as acute chest pain or acute dyspnea.[1,3,4] Based on promising pilot studies,[8–13] we hypothesized that early standardized clinical judgment (ESCJ) including a standardized syncope-specific case report form (CRF) would result in higher diagnostic accuracy as compared to a currently recommended multivariable diagnostic score giving predefined weight to six selected clinical and ECG variables.[14]

We performed an international diagnostic multicenter study using central adjudication of cardiac syncope to test this hypothesis. Secondary aims included direct comparison of ESCJ versus high-sensitivity cardiac troponin I (hs-cTnI) and B-type natriuretic peptide (BNP), two cardiac biomarkers commonly available in the ED, the use of Lasso-regression to identify the variables contributing most to ESCJ[15] and the prognostic performance of the ESCJ.

## METHODS

### Study design, setting and selection of participants

BAsel Syncope EvaLuation Study (BASEL IX) is an ongoing prospective international diagnostic multicenter study enrolling patients from thirteen hospitals in eight countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia and the United States of America). The study is desiged to contribute to improving the management of patients presenting with syncope (ClinicalTrials.gov registry, number NCT01548352).[15–18] Consecutive patients of age 40 years or older, and presenting to the ED with syncope within the last twelve hours were approached and asked to provide written informed consent. Our study intentionally focused on patients 40 years and older, as the risk for a cardiac cause of syncope is very low in younger syncope patients[1,19] and as the complexity of presentation increases with age[20]. In most centers, enrollment was done by study-specific staff, so that the vast majority of patients were enrolled during the day and the evening but not during the night. Those with the final diagnosis of a non-syncopal loss of consciousness (e.g. epilepsy, fall, alcohol intoxication), those lost to follow-up before 1 year

and those in whom no assessment of ESCJ or no ECG was available, were excluded. Patients, in whom a possible cardiac etiology of the index event could neither be clearly documented nor reliably excluded during central adjudication, were excluded from the diagnostic analyses. Sensitivity analyses for the performance of the ESCJ for cardiac syncope were conducted with these patients labelled alternatively as cardiac or non-cardiac syncope in order to test the robustness of our results.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. All patients gave their consent before participation. The authors designed the study, gathered, and analyzed the data according to the STROBE guidelines, wrote the paper, and decided to submit. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

**Clinical assessment, syncope-specific CRF and Early Standardized Clinical Judgment**

Clinical assessment was standardized and recorded on a detailed syncope-specific CRF (Supplemental Fig 1). CRF was composed to integrate key points and red flags highlighted in clinical practice guidelines in place at the time to conduct of this study. The CRF was filled by either study physicians/nurses or the treating clinician and charted in the patient medical record. In addition, ED physicians had access to prior history and comorbidities are recorded in the electronic medical record, the initial laboratory and imaging conducted in the ED as well as the index ECG. Additional tests and treatment as well as the decision to admit or discharge the patient were left to discretion of the clinically responsible physician (See supplemental for details) and the collection of the ESCJ did not interfere with this process. ESCJ for cardiac syncope was quantified by the treating ED physician (resident or attending) between one and two hours after patient presentation to the ED using a visual analogue scale with a likelihood in percentage to the question “How likely has this syncope an underlying cardiac cause?”, thereby reflecting on a semi-qualitative scale ranging from 0 to 100% the subjective risk-estimation done by the ED physician using standardized elements of the anamnesis, prior history, initial ECG, laboratory values and imaging. To assess inter-rater reliability, the medical records of 220 randomly selected patients were reconstructed by study staff to reflect the information available at 90 minutes after admission to the Emergency department (Study-specific CRF, first laboratory

values, ECG, X-rays but no information regarding the final ED impression or subsequent discharge/admission) and the ESCJ was again estimated by two ED physicians with comparable training.

**Endpoints, laboratory methods, follow-up and adjudicated final diagnosis**

The primary endpoint was the diagnosis of cardiac syncope as centrally adjudicated by two independent cardiologists/ED specialists based on all information derived from in-hospital and outpatient cardiac work-up including 1-year clinical follow-up. Patients were contacted 6, 12 and 24 months after discharge by telephone or in written form and information regarding recurrent syncope, hospitalization and cardiac events during follow up was obtained. To determine the final diagnosis for the index syncope, two independent cardiologists/emergency medicine experts reviewed all available medical records from both the clinical and the study-specific data set including all information available up to 1-year follow-up, thereby allowing for possible interval adverse events to inform the index syncope and for results of some diagnostic work-up (such as loop records) to become available when performed (Supplemental methods for details). This adjudication was done for all patients, independently of the initial ESCJ or work-up conducted. In situations of adjudicator disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Teams of adjudicators varied between centers. A total of about twenty seasoned clinicians took part in the adjudication process. Predefined categories for the adjudication included cardiac syncope (ischemic, arrhythmic or cardiovascular origin), reflex syncope, orthostatic syncope, other non-cardiac syncope, and unknown cause of syncope. According to current guidelines,[1] cardiac causes of syncope were defined as arrhythmogenic (brady- or tachycardia), severe structural heart disease, pericardial tamponade, congenital myocardial or valvular anomaly, aortic dissection, or acute pulmonary embolism. It is important to highlight that the presence of cardiac disease (e.g., coronary artery disease) alone was insufficient for the adjudication as cardiac syncope. A syncope of unknown, but non-cardiac origin was adjudicated when a cardiac etiology could be ruled out using all available work-up but the underlying vasovagal or orthostatic pathophysiology was unclear. The prognostic endpoint included Major Adverse Cardiovascular Events (MACE, death, reanimation, life-threatening arrhythmia, implantation of a pacemaker or implantable cardioverter defibrillator, acute myocardial infarction, stroke/transient ischemic attack, intracranial bleeding, valvular

surgery and pulmonary embolism) at 1-year follow up (Supplemental appendix for details). Venous blood samples were drawn upon ED arrival. Details of biomarkers measurements are given in the supplemental.

**Direct comparison with established syncope diagnostic score**

The "Evaluation of Guidelines in Syncope Study" (EGSYS) diagnostic score is based on six clinical and ECG variables, was designed to differentiate between cardiac and non-cardiac causes of syncope;[14] and is a diagnostic score recommended for clinical use in current clinical practice guidelines (Supp. methods for details). The ESCJ was collected and EGSYS score was computed in all patients and were directly compared.

**Subgroup analyses**

Given the high number of sites in Switzerland, three categories of countries were built (Switzerland, other European countries, non-European countries) to assess the consistency within the dataset.

**Statistical analysis**

Areas under the receiver operating characteristic (ROC) curve (AUC) were constructed to assess the diagnostic and prognostic accuracy of ESCJ. Comparisons of AUCs were performed according to DeLong[21]. Impact of the recruiting country on the performance of the ESCJ was assessed through the interaction term. The Youden Index was used to assess the maximal potential effectiveness of the ESCJ, thereby suggesting a cut-off with maximal sensitivity and specificity for the ED physician.

Least absolute shrinkage and selection operator (Lasso) regression was used to investigate which of the variables available early on the ED and recorded in the BASEL IX study contributed most to the ESCJ and which were most relevant to the diagnosis of cardiac syncope. A Lasso regression is a method allowing for both variable selection and regularization. It relies on penalization, meaning shrinking the coefficients of the least important variables to zero. The shrinkage allows for the reliable determination of the variables most predictive of the endpoints. Before regression, missing data were imputed using the "MICE" package in the R statistical software.

Only variables routinely available in the ED within 90 minutes were entered in the Lasso

regression to determine the most important contributors of ESCJ. Details are given in the Supplemental Appendix.

To assess the performance of a model, discrimination and calibration need to be assessed.[22] AUCs are a measure of discrimination, assessing the ability of the model to distinguish a patient with the endpoint (cardiac syncope) from a patient without (non-cardiac syncope). Calibration curves offer a visualization of the agreement between observed and predicted values. The calibration answers the question whether the group of patients labelled with e.g. a 20% risk for cardiac syncope present with a 20% event-rate[23].

Patients in whom the ESCJ performed poorly (ESCJ predicting >70% probability for a cardiac syncope when another diagnosis was adjudicated or ESCJ predicting <30% probability for a cardiac syncope when a cardiac cause was adjudicated) were analyzed as pre-defined subgroups to identify possible pitfalls when using ESCJ.

We assessed the inter-physician variability using intraclass correlation coefficient using a two-way mixed-effect model for absolute agreement.[24]

All hypothesis testing was two-tailed, p-values <0.05 were considered statistically significant. Statistical analyses were performed using the R statistical package (Vienna, Austria).

## RESULTS

### Characteristics of patients

From May 2010 to April 2017, 2006 patients were enrolled (Figure 1), of which 1494 patients were eligible for the diagnostic analysis and 1631 for prognostic analyses. Median age was 71 years, 40% of patients were women, and about half had a history of cardiovascular disease (Supplemental table 1). Patients with a final adjudicated diagnosis of cardiac syncope (n=252, 15.2%) were older, more often had a history of cardiovascular diseases and were more likely to be on cardiovascular medications versus those with other final adjudicated diagnoses. A large number of baseline variables presented with significant overlap between patients with and without cardiac syncope. Other adjudicated diagnoses included reflex (n=665, 40.2%),

orthostatic (n=439, 26.6%), other non-cardiac (n=138, 8.4%) and syncope of unknown, but non-cardiac etiology (n=159, 9.6%). 1103 patients (67% of the cohort) was recruited in Swiss centers, 361 (22%) in European centers and 188 (11%) in America, Australia or New Zealand (Supplemental table 2).

**Diagnostic accuracy of early standardized clinical judgment**

ESCJ of the ED physician, including a standardized syncope-specific CRF for the diagnosis of cardiac syncope as well as comorbidities recorded in the electronic medical record, the index ECG, ED imaging and initial laboratory had very high diagnostic accuracy with an AUC of 0.87 (95%-CI 0.84-0.89), which was significantly higher compared to the EGSYS score (AUC of 0.73 (95%-CI 0.70-0.76)), hs-cTnI (AUC 0.75 (95%-CI 0.72-0.78)) and BNP (AUC 0.75 (95%-CI 0.72-0.78), Figure 2 ). When used on top of the ESCJ, both biomarkers alone or in combination allowed for a significantly better diagnosis of cardiac syncope (ESCJ+BNP AUC of 0.89 (95%-CI 0.87-0.91), ESCJ+hs-cTnI AUC of 0.89 (95%-CI 0.87-0.91), ESCJ+BNP+hs-cTnI AUC of 0.9 (95%-CI 0.88-0.92), all p≤0.001 when compared with ESCJ alone, Figure 2). The very high AUC of the ESCJ was consistent and comparable among recruiting countries ( Figure 3 , p-values for interaction non-significant). The Youden Index, or cut-off of maximal potential effectiveness, lied at an ESCJ of 51.5%. This cut-off allowed for a sensitivity of 78% (95%-CI 0.73, 0.83), a specificity of 84% (95%-CI 0.82, 0.86) and a negative predictive value of 95% (95%-CI 0.94, 0.96).

**Diagnostic sensitivity analyses**

Sensitivity analyses, additionally including patients with a final adjudicated diagnosis of syncope of unknown origin (n=159), when considered to be either of non-cardiac origin or cardiac origin, showed similar ESCJ performance (unknown classified as non-cardiac: AUC 0.85, 95%CI 0.83-0.88, unknown classified as cardiac: AUC 0.83, 95%CI 0.81-0.85).

**Relationship between early standardized clinical judgment on admissions and diagnostics**

There was a significant increase in hospital admission and diagnostics with increasing ESCJ (Supplemental table 3). Relevant discrepancies between ESCJ and patient disposition included the fact that among patients considered at highest risk (ESCJ 75-100%) for cardiac syncope

including arrhythmias, only 37% were admitted to a monitored unit.

**Calibration of early standardized clinical judgment**

As presented in Figure 4 , ESCJ was not well calibrated to the risk of cardiac syncope (Homer-Lemeshow test p-value<0.001). The ED physician (red line) over-estimated the risk for cardiac syncope in comparison with the true observed risk (black line), particularly in patients perceived to be at intermediate risk.

**Determinants of an adjudicated diagnosis of cardiac syncope**

Lasso-regression aiming at the prediction of cardiac syncope identified 16 variables (Supplemental table 4A). These variables included several details on the initial ECG (axis, rhythm, heart rate, AV and branch blocks, ST segment depression, identified arrhythmia, QTc interval), a systolic heart murmur, the presence of lower leg edema, a syncope during exertion, a history of valvular disease or arrhythmia, age, and a clammy sweat before the syncope . The combination of these very early variables performed similarly to ESCJ for the diagnosis of cardiac syncope (Model: AUC of 0.84 (95%-CI 0.82-0.87) versus 0.87 (95%-CI 0.84-0.9), p=0.2) ( Figure 5 ).

**Determinants of Early Standardized Clinical Judgment**

From 113 variables predefined and recorded in this study, which were considered available for the ED physician 90 minutes after presentation (supplemental appendix), lasso-regression aiming at the prediction of the ESCJ identified 22 variables (Supplemental table 4B). The r-squared of the model, indicating how much of the variance could be explained by the model, was 0.3.

**Subgroup analysis of patients in whom Early Standardized Clinical Judgment performed poorly**

ESCJ for cardiac syncope was <30% in 768 patients, 21 (2.7%) of which were finally adjudicated with a diagnosis of cardiac syncope (Supplemental table 5). ESCJ for cardiac syncope was >70% in 275 patients, 117 (42.5%) of which were finally adjudicated with a non-cardiac syncope.

In patients incorrectly classified as low-risk, the model using variables available very-early in the ED estimated a median risk of 33.6% (IQR 24.3-46.0%) while the ESCJ estimated a significantly

lower median risk of 20% (IQR 20-20%, Wilcoxon-test p-value for comparison=0.007).

In patients incorrectly classified as high-risk, the model using variables available very-early in the ED estimated a median risk of 4.2% (IQR 1.5-10.8%) while the ESCJ estimated a significantly higher median risk of 96.6% (IQR 90-100%, Wilcoxon-test p-value for comparison= <0.001).

Concentrations of hs-cTnI and BNP were respectively significantly higher/lower in patients incorrectly classified as being at low- or high-risk for cardiac syncope respectively, as compared to patients correctly classified by the ESCJ (Supplemental Figure 2 ).

**Prognostic accuracy of the early standardized clinical judgement**

At 1 year, 307 (18.8%) patients experienced a MACE. The accuracy of the ESCJ for this endpoint as given by the AUC was 0.75 (0.71-0.78, Supplemental Figure 3 ).

**Interrater reliability of the early standardized clinical judgement**

The intra-class correlation coefficient for the ESCJ was 0.798 (95%-CI 0.745-0.841, p<0.001), indicating a good inter-rater reliability[24].

## DISCUSSION

This large international diagnostic multicentre study was performed to test the hypothesis that ESCJ of the ED physician for cardiac syncope including a standardized syncope-specific CRF would result in higher diagnostic accuracy as compared to a currently recommended multivariable diagnostic score (EGSYS).

We report **six** major findings.

**First**, ESCJ of the ED physician including a standardized syncope-specific CRF had high diagnostic accuracy, which was significantly higher compared to the EGSYS score. In contrast to EGSYS score, which gives predefined weight to six clinical and ECG variables, ESCJ avoids scoring points and allows physician to individually integrate all clinical and ECG information available. **Second**, diagnostic accuracy of ESCJ was consistently high and comparable among different recruiting countries. **Third**, ESCJ also outperformed well-validated cardiac biomarkers quantifying cardiomyocyte injury (hs-cTnI) and hemodynamic cardiac stress (BNP)[15]. This is in contrast to the relative importance of these diagnostic tools in the two other presenting symptoms commonly underlying acute cardiac disorders: acute chest pain and acute dyspnea.

In the latter, the diagnostic accuracy of hs-cTnT/I and BNP is substantially higher as compared to clinical judgment without these biomarkers.[25–27] However, biomarkers did show a benefit when used on top of clinical judgment. **Fourth**, while the ESCJ performed well for discrimination (differentiating patient with a high risk versus patients with a low risk for cardiac syncope, as represented in the AUC), calibration was suboptimal with ED physicians systematically overestimating the probability of cardiac syncope. At least in part, this overestimation may be related to incomplete knowledge of the prevalence of cardiac syncope among patients presenting with syncope to the ED or possibly to the tendency of the ED physicians to consider worst-case scenario with the aim to rule these deadly diagnoses out.[15–18] While overestimating the risk for cardiac syncope possibly leads to a better patients safety, it also leads to a high number of admissions and associated substantial costs. **Fifth**, in full agreement with the systematic overestimation of the probability for cardiac syncope, patient disposition was only partly related to ESCJ. Some patients were classified as high-risk by the ESCJ but subsquently discharged directly from the ED. This likely reflects the acquisition of further reassuring diagnostic work-up in the ED, a decision to admit or discharge taken by a second physician, patient refusal of hospital admission despite medical advice as well as lack of availability of hospital beds. **Sixth**, a multivariable model based on a rather large number of clinical variables available very-early after patient presentation to the ED achieved comparable diagnostic accuracy versus ESCJ. This further highlight the level of detail necessary for an accurate diagnosis of cardiac syncope. However, despite the precise recording of a large number of patient's characteristics, details from the syncopal event and from the clinical examination, ESCJ of the ED physician will always benefit from information, which is difficult to record in a predefined CRF, such as the gravity of comorbidities, their timely occurrence or uncertainty regarding some pieces of information. These subtleties possibly explain the large residual variance (low r-square) that the model characterizing ESCJ could not explain.

These findings corroborate and extend previous pilot studies documenting that clinical judgment of the ED physician for a composite of serious adverse outcomes had high prognostic accuracy.[8–12] Our findings also highlight the substantial diagnostic value of detailed patient and possibly also bystander history regarding the exact details of the syncope episode as recorded in the syncope-specific CRF. While this CRF does contain a significant number of data points, it

allows to highlight and summarize the variables most important for patients evaluation among the enormous amount of data available to the ED physician. This may have direct clinical consequences, as the implementation into routine clinical care of this simple tool, possibly within the electronic medical record, can be expected to increase the diagnostic accuracy of the ED physician, reduce the time to diagnosis as well as time to decision regarding patient allocation, and thereby also reduce overall treatment costs.

Based on our data, the generalizability of these findings seems very high. ESCJ for cardiac syncope was obtained from the treating ED physician including residents. Therefore, the remarkable performance of this tool does not seem restricted to physicians highly specialized into the management of syncope. In the present analysis, it achieved good and consistent accuracy when applied in different health care settings on different continents and showed good inter-rater reliability.

Syncope includes a heterogeneous group of underlying etiologies and previous attempts to focus on a small number of variables[14] to derive diagnostic tools reached only moderate accuracy. The difficulty to separate cardiac from non-cardiac syncope is evident when observing the large overlap of baseline characteristics, past medical history or chronic medications patients of the present cohort displayed upon presentation. Accordingly, the short EGSYS score, which aimed at guiding physicians in their diagnosis, showed a lower diagnostic accuracy as compared to ESCJ in this study.

The limited discriminative power of the EGSYS-score is likely due to its reductive character and simplicity: To allow for rapid calculation, this score summarizes together several components of the ECG and evaluates few symptoms related to the event. However, the findings of this study indicate that a larger number of variables would be required to achieve a very-early triage with a discrimination similar to the one of ESCJ.

Several limitations need to be taken into account when interpreting these findings. First, ESCJ for cardiac syncope at 60 to 120 minutes included information derived from a standardized syncope-specific CRF. Although we used all information at the initiation of the BASEL IX study to design this standardized syncope-specific CRF, it is conceivable that updating this standardized syncope-specific CRF using novel information derived from recent studies[15–18] might allow to achieve even higher diagnostic accuracy. Including information on the

expected prevalence of cardiac syncope might allow to also improve calibration. Second, unfortunately this study did not record the exact medical background of the treating ED physicians, which were asked to quantify their ESCJ for cardiac syncope. Therefore, we cannot assess the impact of differences in medical training on diagnostic accuracy of ESCJ and EGSYS for cardiac syncope. Third, despite using a very stringent methodology of central adjudication of the final diagnosis by two independent cardiologists/ED specialists based on all information derived from in-hospital and outpatient cardiac work-up including 1-year clinical follow-up, it is possible that a small number of patients might have been misclassified. This would have led to an underestimation of the true diagnostic accuracy of ESCJ. Fourth, We cannot quantify the relative contribution that the standardized CRF had for ESCJ. Fifth, despite being one of the largest multicenter study performed on the topic, recruitment from one country (Switzerland) contributed more than half of patients. Therefore the sample might still have been undersized for demonstrating consistency in other health care systems and for some subgroup analyses.

Finally, the findings of this study are specific to patients presenting with syncope to the ED. Further studies are required to evaluate the diagnostic accuracy of ESCJ including a standardized syncope-specific CRF in settings with substantially lower (general practitioner) or higher (cardiology department) prevalence of cardiac syncope.

In conclusion, ESCJ including a standardized syncope-specific CRF has very high diagnostic accuracy and outperforms the EGSYS-score, hs-cTnI, and BNP.

**Additional BASEL IX Investigators[b] and Contributors to this manuscript to be listed in Pubmed:**

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**CONFLICT OF INTERESTS DISCLOSURES**

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and decided to publish. Drs. du Fay de Lavallaz, Badertscher, Zimmermann and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers.

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All other authors declare that they have no conflict of interest with this study.

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**Figure legends:**

**Figure 1** – Patient chart flow

**Figure 2** –Performance of the Early standardized Clinical Judgement (ESCJ) of the ED physician including a structured syncope-specific case report form in comparison with the

EGSYS Score, hs-cTnI and BNP. CRF = Case Report Form, Hs-cTnI = High-sensitivity Troponin I, BNP = B-type natriuretic peptide, CI = Confidence interval, EGSYS = Evaluation of Guidelines in Syncope Study.

**Figure 3** – Diagnostic accuracy of Early standardized Clinical Judgement (ESCJ) of the ED physician including a syncope-specific case-report form classified according to the recruiting country. Vertical dotted line : Overall ESCJ performance.

**Figure 4** – Calibration curve representing the accuracy of the Early standardized Clinical Judgment (ESCJ) of the ED physician to estimate the risk for cardiac syncope (red line) compared with the true observed risk (black line). CI = Confidence interval. The Hosmer-Lemeshow p-value confirms that the prediction of the ED physician significantly differs from the optimal calibration.

**Figure 5** – Accuracy of the model using the variables highlighted as important for the diagnosis of cardiac syncope by the lasso regression and accuracy of the early standardized clinical judgement (ESCJ) of the ED physician. P-value was calculated according to DeLong. CI = 95% confidence interval.

**Figure 1**

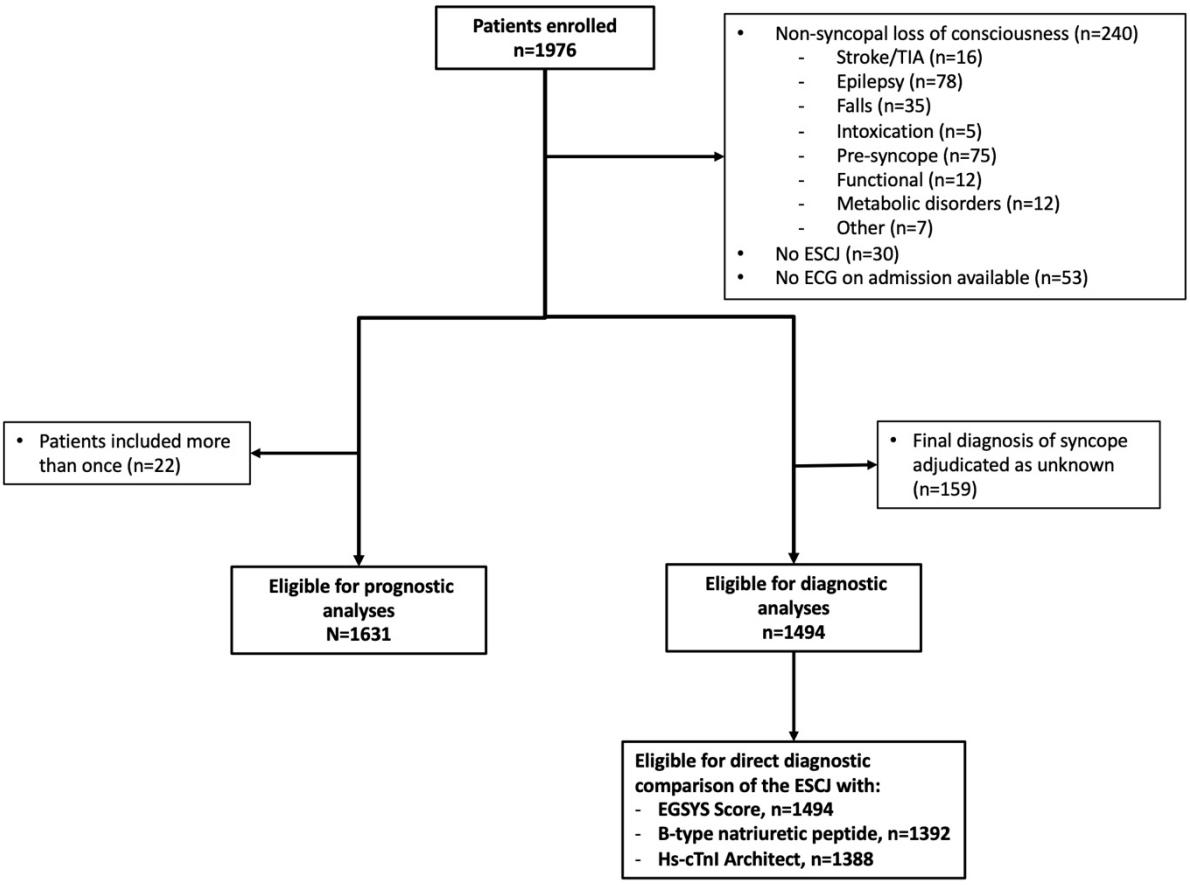
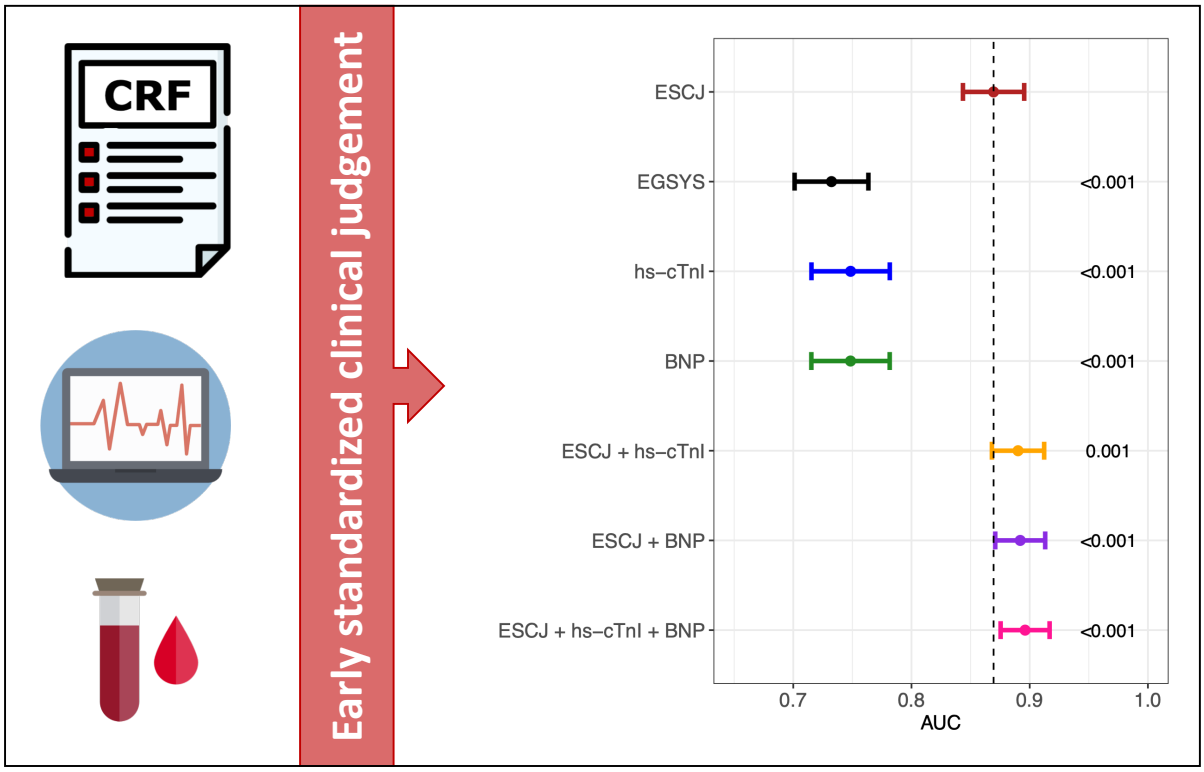

Patients enrolled
n=1976
• Non-syncopal loss of consciousness (n=240)
- Stroke/TIA (n=16)
- Epilepsy (n=78)
- Falls (n=35)
- Intoxication (n=5)
- Pre-syncope (n=75)
- Functional (n=12)
- Metabolic disorders (n=12)
- Other (n=7)
• No ESCJ (n=30)
• No ECG on admission available (n=53)
• Patients included more than once (n=22)
• Final diagnosis of syncope adjudicated as unknown (n=159)
Eligible for prognostic analyses
N=1631
Eligible for diagnostic analyses
n=1494
Eligible for direct diagnostic comparison of the ESCJ with:
- EGSYS Score, n=1494
- B-type natriuretic peptide, n=1392
- Hs-cTnI Architect, n=1388

**Figure 2**


CRF
Early standardized clinical judgement
ESCJ
EGSYS
hs–cTnI
BNP
ESCJ + hs–cTnI
ESCJ + BNP
ESCJ + hs–cTnI + BNP
<0.001
<0.001
<0.001
0.001
<0.001
<0.001
0.7
0.8
0.9
1.0
AUC

## Figure 3

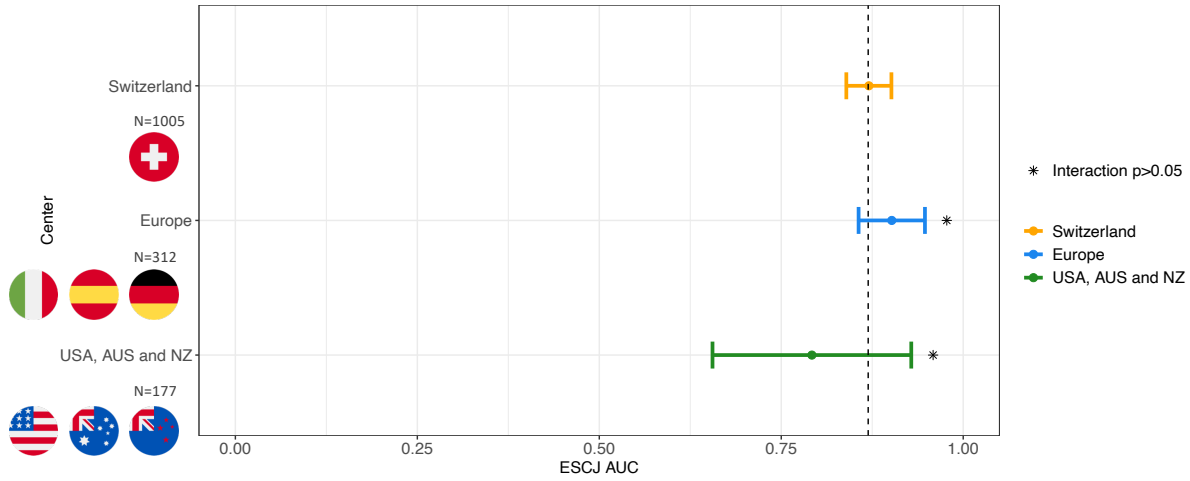

Switzerland
N=1005
Center
Europe
N=312
USA, AUS and NZ
N=177
0.00
0.25
0.50
0.75
1.00
ESCJ AUC
Interaction p>0.05
Switzerland
Europe
USA, AUS and NZ

**Figure 4**

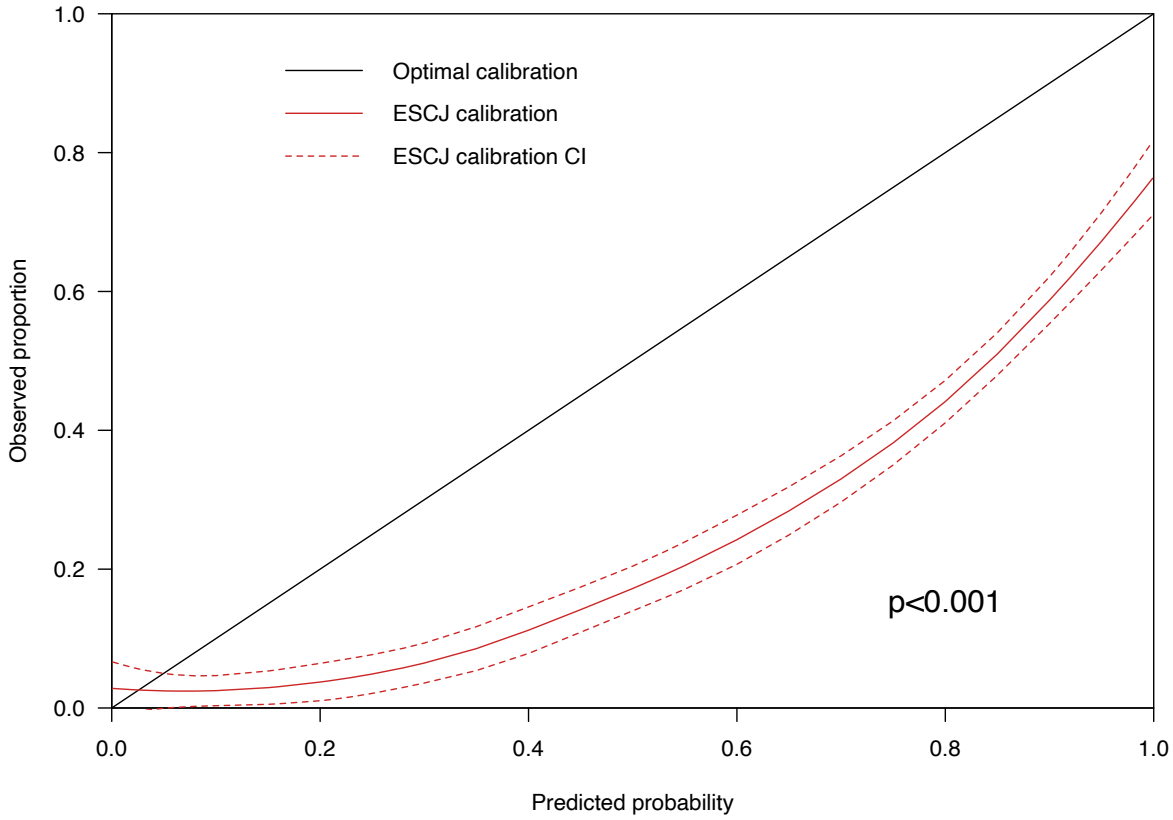
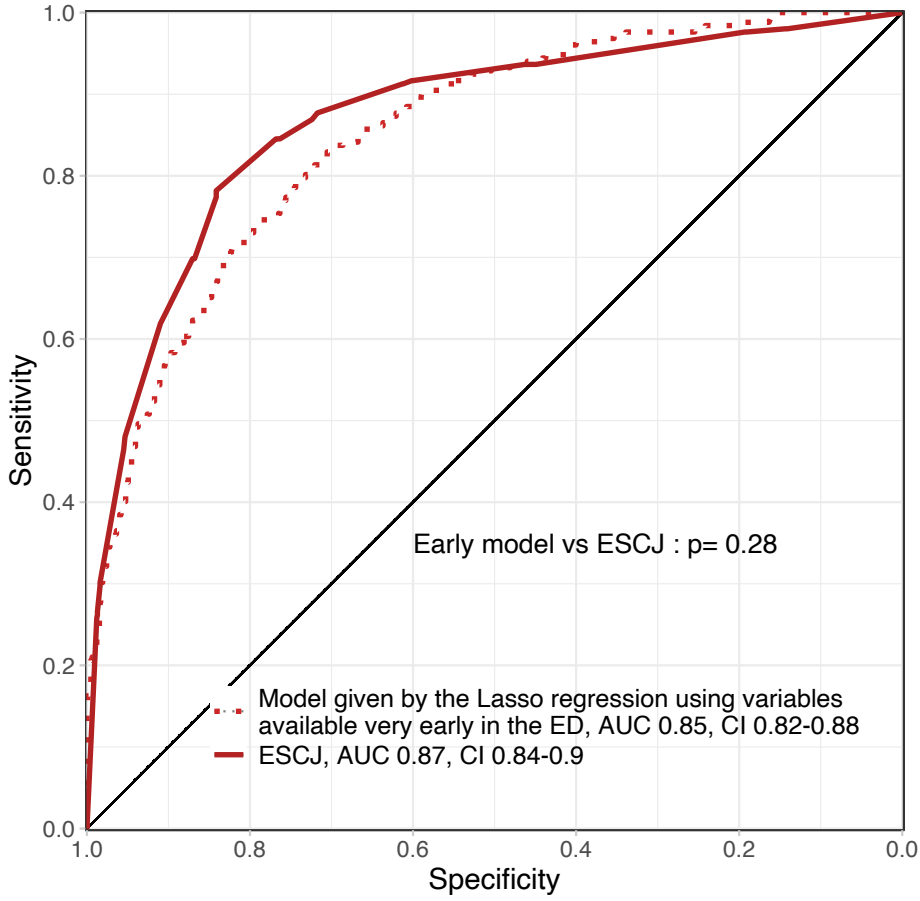

Optimal calibration
ESCJ calibration
ESCJ calibration CI
p<0.001
Observed proportion
Predicted probability
0.0
0.2
0.4
0.6
0.8
1.0

**Figure 5**


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Specificity
Early model vs ESCJ : p= 0.28
Model given by the Lasso regression using variables available very early in the ED, AUC 0.85, CI 0.82-0.88
ESCJ, AUC 0.87, CI 0.84-0.9

# Supplemental Material

# Supplemental Appendix – Performance of the Early Clinical Judgement for the diagnosis of syncope on the Emergency Department

## Supplemental methods

### Clinical assessment

All patients underwent a clinical assessment, as recorded on a study-specific CRF (supp. Fig 1), that included standardized and detailed assessment of predefined details of medical history, including previous syncope events and circumstances of current syncope, vital signs, physical examination, routine laboratory tests, radiologic testing, and a 12-lead ECG. Additionally, patients may have also undergone 24-hour ECG, external or implantable loop device, cardiac exercise test, Shellong test, tilt table testing, coronary angiography, continuous rhythm monitoring, pulse oximetry, echocardiography, results from device controls (e.g. pacemaker) or electrophysiological examinations, and recording of findings of further investigations during recurrent hospitalization or ambulant treatment. Additional tests and treatment of patients were left to discretion of the clinically responsible physician.

### Follow up and adjudication of the final syncope diagnosis

During the follow-up, information regarding recurrent syncope, hospitalization and cardiac events during follow up was furthermore obtained from the patient's hospital notes, the family physician's records and national mortality registries, where available.

The first step in the adjudication process was to decide whether there was syncope or not. The clinical data set included data from the clinical assessment, while study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, and physical examination, as well as at least 12 months follow-up. If the criteria for a true syncope were not fulfilled, a distinction between the following non-syncopal disorders was made: pre-syncope; falls; stroke/TIA; epilepsy; metabolic disorders: e.g. hypoglycaemia, hypoxia, hyperventilation; intoxication: e.g. alcohol, benzodiazepines, opiates; functional (psychogenic pseudosyncope); others.

The classification of syncope is based on pathophysiological considerations. The following predefined differential diagnoses were used:

1) Cardiac syncope: We distinguished between:
    a. Arrhythmia as primary cause: Arrhythmias are the most common cause of syncope; Bradycardia: sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction or drug-induced; Tachycardia: supraventricular or ventricular.
    b. Structural heart disease: structural heart diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase output. However, in some cases syncope may not solely be the result of restricted cardiac output, but be in part due to an inappropriate reflex. However, when a structural heart disease was the primary cause or contributed most to syncope, it was classified as cardiovascular syncope.
    c. Others: pulmonary embolism, acute aortic dissection, pulmonary hypertension or any other cause for a cardiovascular syncope.
2) Reflex (neutrally-mediated) syncope: This syncope is characterized by cardiovascular reflexes which are normally useful in controlling circulation but become intermittently inappropriate in response to a trigger. The reflex results in vasodilation and/or bradycardia which lead to a fall in arterial blood pressure and consequently to cerebral hypoperfusion. Identifying a trigger is central when diagnosing a reflex syncope. Typically symptoms as lightheadedness, nausea, sweating, weakness or visual disturbances precede reflex syncope. We distinguished between:
    a. Vasovagal: "common faint", triggered by emotional distress/ pain or mediated by orthostatic stress.

   b. Situational: refers to reflex syncope associated with some specific circumstances, e.g. post-micturition, post-prandial, gastrointestinal stimulation, cough.
   c. Carotid sinus syncope: triggered by mechanical manipulation of the carotid sinus. It can be diagnosed by carotid sinus massage.
   d. Atypical forms: reflex syncope occurring with uncertain or apparently absent triggers.
3) Syncope due to orthostatic hypotension: Orthostatic hypotension is defined as an abnormal decrease in systolic blood pressure after changing from supine to standing position. Key can be syncope immediately after standing up or a pathological Schellong test. We distinguished between:
   a. Primary autonomic failure: There is an autonomic failure which is clearly a primary part of Parkinson syndrome as idiopathic Parkinson disease or atypical Parkinson syndrome (multiple system atrophy, progressive supranuclear oculomotoric paresis, corticobasal degeneration or lewy body dementia).
   b. Secondary autonomic failure: autonomic failure may be due to circumstances such as diabetes, uraemia, amyloidosis or spinal cord injuries
   c. Drug-induced orthostatic hypotension: orthostatic hypotension is due to drugs which can lead to orthostatic hypotension such as diuretics, antidepressants, vasodilators, alcohol
   d. Volume depletion: orthostatic hypotension is caused by a hypovolemia due to haemorrhage, diarrhoea, vomiting or fever
   e. Others: sometimes the pathophysiology remains unclear.
4) Others, non-cardiac syncope: Sometimes the underlying pathophysiological mechanism of syncope remains unclear, but a cardiac syncope is ruled-out.
5) Syncope of unknown etiology (cardiac syncope possible): the etiology of syncope still remained unknown and a cardiac syncope was considered to be a possible cause.

## Prognosis

Patients were contacted at 6 months, 1 year, 2 years and 5 years after the initial event per phone or letter and records were required at each time point from outside hospitals, patients physicians and national registers, when available.

Overall MACE included death, reanimation, life-threatening arrhythmia, implantation of a pacemaker or implantable cardioverter defibrillator (ICD), acute myocardial infarction, stroke/transient ischemic attack (TIA), intracranial bleeding, valvular surgery and pulmonary embolism. Life-threatening arrhythmia was defined as ventricular fibrillation, sustained ventricular tachycardia (VT) [>120 beats/min], ventricular pause [>3s], ventricular standstill, or asystole, consistent with the definition given in previous syncope research[1]. Acute myocardial infarction was defined according to the Third Universal Definition[2].

## Laboratory methods

Venous blood samples were drawn via a peripheral intravenous line upon ED arrival, plasma was then immediately processed and frozen at -80°C until assayed. BNP measurements were performed using the Architect BNP assay[3] and hs-cTnI using the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories)[4]. The laboratory team who measured biomarkers was blinded to patient, clinical and diagnostic assessment, discharge and adjudicated diagnosis.

BNP measurements were performed by use of the Architect BNP assay[3]. The assay's LoB is 0.6 ng/l, LoD is 1.4 ng/l, and LoQ is 3.4 ng/l at 20% CV. There is no hook effect up to 100,000 ng/l. Total imprecision is < 10% for concentrations 4.5 ng/l and higher. In this study,

controls run on each assay plate provided inter-assay precision of 8.3% at 4.5 ng/l and 4.1% at 218 ng/l.
Hs-cTnI Architect measurements were performed at the University Hospital of Basel using the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories, Abbott Park, IL). This assay has a 99th percentile concentration of 26.2 ng/L with a corresponding CV of <5% and an LoD of 1.9 ng/L[4].

## Scores

### *Evaluation of Guidelines in Syncope Study (EGSYS)[5] diagnostic score components*

The point score is found as the sum of the following risk factors:

- Palpitations: 4
- Abnormal ECG/Cardiopathy: 3
- Effort Syncope: 3
- Syncope in supine position: 2
- Neurovegetative prodromes: -1
- Precipitating and predisposive factors: -1

A score greater than or equal 3 implies an increased risk for cardiac syncope.

### *Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL)[6] risk score components*

The point score is found as the sum of the following risk factors:

- age >65 years: + 1
- cardiovascular disease in clinical history +1
- syncope without prodromes: +1
- abnormal electrocardiogram +1

The primary end point was death from any cause within 12 months of the initial evaluation in the ED.

### *Canadian Syncope Risk score[7]*

The point score is found as the sum of the following risk factors:

- Vasovagal predisposition: -1
- History of heart disease : +1
- Any ED systolic blood pressure (BP) <90 or >180mmHg : +2
- Troponin elevated (>99%ile normal population) +2
- Abnormal QRS Axis (<-30 or >100) : +1
- QRS duration >130 milliseconds : +1
- Corrected QT interval >480miliseconds: +2
- Diagnosis in the ED : Vasovagal syncope : -2
- Diagnosis in the ED : Cardiac syncope : +2

The BASEL IX study only recorded systolic blood pressure measured upon admission.
The primary end point was death or MACE (as defined in the BASEL IX study) within 30 days of the initial evaluation in the ED.

### *Score by Sun et al.[8]*

The point score is found as the sum of the following risk factors:

- Age >90 years : +1
- Male gender : +1
- History of arrhythmia : +1

- Triage systolic blood pressure >160mmHg : +1
- Abnormal electrocardiogram : +1
- Abnormal troponin I : +1
- Near-syncope : -1

The primary end point was death or MACE (as defined in the BASEL IX study) within 30 days of the initial evaluation in the ED.
The BASEL IX cohort did not recruit patients with near-syncope, this point was therefore ignored during score validation.

### Lasso (Least absolute shrinkage and selection operator) regression

A lasso regression is a statistical method that performs both variable selection and regularization. This implies mathematical procedures that select the preferred level of model complexity to enhance the prediction accuracy, interpretability and generalization of the statistical model[9]. It is also used to make prediction models in a dataset with many and often inter-correlated independent variables. Thus, lasso regression has important statistical features to help assess the association between many variables and clinical outcomes[10].
The analysis was conducted using the package "glmnet" in the R statistical software.
To select variables, the lasso uses a "tuning parameter" lambda, which determines the level of shrinkage. To select this tuning parameter while avoiding model overfitting, we performed cross-validation of a grid of lambda values. The cross-validation estimates the expected generalization error for each lambda. We selected a lambda within 1.5 standard deviation of the lambda minimizing the generalization error to limit model complexity and avoid overfitting[11].

*Variables entered in the lasso regressions :*

| Variables used for the lasso-regressions | Variable levels | Entered in the lasso regression aiming at diagnosing cardiac syncope very early on the ED | Entered in the lasso regression aiming at explaining the ESCJ |
|---|---|---|---|
| Age | (continuous) | ✓ | ✓ |
| Sex | Male | ✓ | ✓ |
| | Female | | |
| Family history of CAD | No | ✓ | ✓ |
| | Yes | | |
| Family history of SCD | No | ✓ | ✓ |
| | Yes | | |
| Family history of stroke | No | ✓ | ✓ |
| | Yes | | |
| History of MI | No | ✓ | ✓ |
| | Yes | | |
| History of Bypass | No | ✓ | ✓ |
| | Yes | | |
| Valvular disease | No | ✓ | ✓ |
| | Yes | | |
| History of arrhythmia | No | ✓ | ✓ |

| | | | |
|---|---|---|---|
| | Yes | | |
| Pacemaker | No | ✓ | ✓ |
| | Yes | | |
| ICD/CRT | No | ✓ | ✓ |
| | Yes | | |
| History of hypertension | No | ✓ | ✓ |
| | Yes | | |
| Diabetes | No | ✓ | ✓ |
| | Yes | | |
| Hypercholesterolemia | No | ✓ | ✓ |
| | Yes | | |
| GI Bleeding in the last week | No | ✓ | ✓ |
| | Yes | | |
| Number of previous syncope | None | ✓ | ✓ |
| | 1 | | |
| | 2 | | |
| | 3 | | |
| | More than 3 | | |
| History of ICB | No | ✓ | ✓ |
| | Yes | | |
| History of stroke | No | ✓ | ✓ |
| | Yes | | |
| History of epilepsy | No | ✓ | ✓ |
| | Yes | | |
| History of DVT/PE | No | ✓ | ✓ |
| | Yes | | |
| History of PAD | No | ✓ | ✓ |
| | Yes | | |
| History of depression | No | ✓ | ✓ |
| | Yes | | |
| Medication : Aspirin | No | ✓ | ✓ |
| | Yes | | |
| History of psychiatric disease | No | ✓ | ✓ |
| | Yes | | |
| History of smoking | Never | ✓ | ✓ |
| | Sporadically | | |
| | Active smoker | | |
| | Ex-smoker | | |
| History of CHD | No or NYHA I | ✓ | ✓ |
| | NYHA II to NYHA IV | | |
| History of CAD | No | ✓ | ✓ |
| | Yes | | |
| Previous PCI | No | ✓ | ✓ |
| | Yes | | |
| Medications: Anti-coagulants | No | | |

| | | | |
|---|---|---|---|
| | Yes | ✓ | ✓ |
| Medications: Diuretics | No | ✓ | ✓ |
| | Yes | | |
| Medications: Digitalis | No | ✓ | ✓ |
| | Yes | | |
| Medications: Nitrates | No | ✓ | ✓ |
| | Yes | | |
| Medications: Beta-blockers | No | ✓ | ✓ |
| | Yes | | |
| Medications: Anti-arrhythmics | No | ✓ | ✓ |
| | Yes | | |
| Medications: Statins | No | ✓ | ✓ |
| | Yes | | |
| Medications: Anti-depressants | No | ✓ | ✓ |
| | Yes | | |
| Medications: ACE | No | ✓ | ✓ |
| | Yes | | |
| Medications: Calcium antagonists | No | ✓ | ✓ |
| | Yes | | |
| Medications: platelet inhibitors | No | ✓ | ✓ |
| | Yes | | |
| Medications: Alphablockers | No | ✓ | ✓ |
| | Yes | | |
| Medications: Antiepileptics | No | ✓ | ✓ |
| | Yes | | |
| Medications: Analgesics | No | ✓ | ✓ |
| | Yes | | |
| Medications: PPI | No | ✓ | ✓ |
| | Yes | | |
| ECG : QRS | (continuous) | ✓ | ✓ |
| ECG : PQ | (continuous) | ✓ | ✓ |
| ECG : Heart rate | Normocard | ✓ | ✓ |
| | Tachycard (>100bpm) | | |
| | Bradycard (<45bpm) | | |
| ECG : Long QT | Normal | ✓ | ✓ |
| | Long (≥460ms) | | |
| ECG : AV block | None | ✓ | ✓ |
| | AV block I° or Mobitz Type I | | |
| | AV block Mobitz Type II or III° | | |
| ECG : Axis[1] | Normal (Normal or left | ✓ | ✓ |

[1] All ECG parameters labelled with a « * » were determined on the index case ECG and in comparison with a previous ECG, if available. If no previous ECG was available, any abnormalities on the index case ECG was considered new.

| | | | |
|---|---|---|---|
| | axis) | | |
| | Abnormal (Right, extreme left or extreme right axis) | | |
| | Abnormal but previously known | | |
| ECG : ST depression * | None | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG : ST elevation* | None | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG : Arrhythmia* | None | ✓ | ✓ |
| | Present (Ventricular extrasystoles, couplets, triplets, runs, non-sustained VT) | | |
| | Present but previously known | | |
| ECG: Complete bundle branch block* | None | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG: Incomplete bundle branch block* | None | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG: Negative T waves* | No | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG : Q waves* | No | ✓ | ✓ |
| | Present | | |
| | Present but previously known | | |
| ECG : LV hypertrophy | No | ✓ | ✓ |
| | Yes | | |
| ECG : Rhythm | Normal (Sinus rhythm) | ✓ | ✓ |
| | Abnormal (Atrial fibrillation or flutter, ventricular or atrial ectopy, PM rhythm) | | |
| Laboratory : Leucocytes | Normal | ✓ | ✓ |
| | High ($\geq 10^3/\mu L$) | | |
| | Very high ($\geq 50^3/\mu L$) | | |
| Laboratory : Hemoglobin | Normal | ✓ | ✓ |
| | Anemia (<110 g/L for female, <130 g/L for male) | | |
| | Severe anemia (<70 g/L | | |

| | | | |
|---|---|---|---|
| | for female, <90 g/L for male) | | |
| Laboratory : Hematocrit | Normal | ✓ | ✓ |
| | Low (36% for female, <38% for male) | | |
| Laboratory : Sodium | Normal | ✓ | ✓ |
| | Low (<135mEq/L) | | |
| | Very low (<120 mEq/L) | | |
| Laboratory : Potassium | Normal | ✓ | ✓ |
| | Hypo (<3.6 mmol/L) | | |
| | Hyper (>5 mmol/L) | | |
| | Severe hypo (<2.5 mmol/L) | | |
| | Severe hyper (>6 mmol/L) | | |
| Laboratory : Creatinine | Normal | ✓ | ✓ |
| | High (>80 mmol/L) | | |
| Syncope : Before : Nausea | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Clammy sweat | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Palpitations | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Chest pain | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Blurred vision | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Dizziness | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Before : Dyspnea | No | ✓ | ✓ |
| | Mild | | |
| | Moderate | | |
| | Severe | | |
| | Very severe | | |
| Syncope : Before : Weakness | No | ✓ | ✓ |
| | Mild | | |
| | Severe | | |
| Syncope : Before : Pain | No | ✓ | ✓ |
| | Headache | | |
| | Backache | | |
| | Chest pain | | |
| | Bellyache | | |
| | Due to injury | | |
| | Other | | |
| Syncope : After : Nausea | No | ✓ | ✓ |
| | Yes | | |
| Syncope : After : Clammy sweat | No | ✓ | ✓ |

| | | | |
|---|---|---|---|
| | Yes | | |
| Syncope : After : Palpitations | No | ✓ | ✓ |
| | Yes | | |
| Syncope : After : Chest pain | No | ✓ | ✓ |
| | Yes | | |
| Syncope : After : Dizziness | No | ✓ | ✓ |
| | Yes | | |
| Syncope : After : Dyspnea | No | ✓ | ✓ |
| | Mild | | |
| | Moderate | | |
| | Severe | | |
| | Very severe | | |
| Syncope : After : Pain | No | ✓ | ✓ |
| | Headache | | |
| | Backache | | |
| | Chest pain | | |
| | Bellyache | | |
| | Due to injury | | |
| | Other | | |
| Syncope : After : Weakness | No | ✓ | ✓ |
| | little | | |
| | distinct | | |
| Syncope : After : Awakening | awake | ✓ | ✓ |
| | tired | | |
| | disoriented | | |
| Syncope : Position : Supine | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Position : Sitting | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Position : Orthostatic | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Position : Standing | No | ✓ | ✓ |
| | Yes | | |
| Syncope : During exertion | No | ✓ | ✓ |
| | Yes | | |
| Syncope : Accompanied by fall | No | ✓ | ✓ |
| | Yes | | |
| Syncope : During : Incontinence | No | ✓ | ✓ |
| | Yes | | |
| Status : Signs of infection | No | ✓ | ✓ |
| | Yes | | |
| Status : Head trauma | No | ✓ | ✓ |
| | Yes | | |
| Status : Neurological deficit | No | ✓ | ✓ |
| | Yes | | |

| | | | |
|---|---|---|---|
| Status : Lung rales on auscultation | No | ✓ | ✓ |
| | Right | | |
| | Left | | |
| | Both sides | | |
| Status : Systolic heart murmur | None or 1/6 | ✓ | ✓ |
| | 2-3/6 | | |
| | 4-6/6 | | |
| Status : Diastolic heart murmur | None or 1/6 | ✓ | ✓ |
| | 2/6 to 6/6 | | |
| Status: Edema | No | ✓ | ✓ |
| | Yes | | |
| Status: Injury | No | ✓ | ✓ |
| | Yes | | |
| VP: Fever | No fever | ✓ | ✓ |
| | Fever (>38°C) | | |
| VP: Oxygen saturation | Normal oxygen saturation | ✓ | ✓ |
| | Abnormal oxygen saturation (<95%) | | |
| VP: Tension | Normal | ✓ | ✓ |
| | Hypertensiv (Syst. BP >160mmHg) | | |
| | Hypotensiv (Syst. BP <90mmHg) | | |
| Vigilance | Normal | ✓ | ✓ |
| | Reduced | | |
| Laboratory: CRP | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured : Abnormal (≥10 mg/L) | | |
| Laboratory : Glucose | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: Hyperglycaemia (>6.1 mmol/L) | | |
| | Measured: Hypoglycaemia (<3.8 mmol/L) | | |
| Laboratory : D-Dimers | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: Abnormal (≥0.5mg/L) | | |
| Laboratory : CK | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: Abnormal (≥200U/L) | | |
| Laboratory : pH | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: too high (≥7.430) | | |

| | | | |
|---|---|---|---|
| | Measured: too low (<7.380) | | |
| Laboratory : BNP | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: Abnormal (≥300pg/mL) | | |
| Laboratory : Toxicology | Not assessed | | ✓ |
| | Assessed: Normal | | |
| | Assessed: Abnormal | | |
| Schellong | Not assessed | | ✓ |
| | Normal | | |
| | Pathologic | | |
| Laboratory : Troponin | Not measured | | ✓ |
| | Measured: Normal | | |
| | Measured: Abnormal (≥respective assay's cut-off) | | |
| Chest Xray | Not assessed | | ✓ |
| | Normal | | |
| | Pathologic | | |
| Status: Blood pressure difference | Not assessed | | ✓ |
| | Normal | | |
| | Pathologic | | |
| Status: Signs of bleeding | Not assessed | | ✓ |
| | Assessed, no signs of GI bleeding or negative DR examination | | |
| | Assessed, signs of GI bleeding or positive DR examination | | |

BNP : B-type natriuretic peptide; CK: Creatine Kinase; DR : Digital rectal, GI : gastrointestinal, VP : Vital parameters

### Imputation:

We imputed missing values using the "MICE" package in the R-statistical software using Multivariate imputation by chained Equations. A predictor matrix was created with a mean number of predictors of 20.4.

The imputed variables as well as the number and percentage of missing values are presented in the table here under. The highest percentage of missing was 10.47% for one variable. Missing values stemming from variables where the decision of the ED physician to measure or obtain them played a major role were not imputed. For instance, if troponin was not ordered during ED work-up, no value was imputed and the value of "not ordered" was considered as a level. This procedure was applied for laboratory measurements and clinical examinations which are not systematically ordered or realized for syncope work-up (For instance Troponin, BNP, Schellong test, Chest Xray).

Baseline characteristics, laboratory values, details of the syncopal events and adjudicated diagnosis were used as predictors.

| Number and percentage of missing per imputed variable. | | |
|---|---|---|
| Variable | Nr of missings | Percentage of missing |
| Family history of CAD | 139 | 8.41 |
| Family history of SCD | 134 | 8.11 |
| Family history of Stroke or TIA | 173 | 10.47 |
| Known valvular disease | 38 | 2.30 |
| History of arrhythmia | 25 | 1.51 |
| Pacemaker | 11 | 0.67 |
| ICD or CRT | 12 | 0.73 |
| History of hypertension | 6 | 0.36 |
| Known Diabetes | 5 | 0.30 |
| History of hypercholesterolemia | 56 | 3.39 |
| History of GI bleeding | 64 | 3.87 |
| Number of previous syncopes | 39 | 2.36 |
| History of ICB | 10 | 0.60 |
| History of stroke | 11 | 0.67 |
| History of epilepsy | 11 | 0.67 |
| History of DVT or PE | 5 | 0.30 |
| History of PAD | 29 | 1.75 |
| History of psychiatric disorder | 94 | 5.69 |
| Smoking | 21 | 1.27 |
| Known chronic HF | 37 | 2.24 |
| Known CAD | 22 | 1.33 |
| QTc interval | 1 | 0.06 |
| PQ interval | 1 | 0.06 |
| Laboratory: Leucocytes | 13 | 0.79 |
| Laboratory: Hemogobin | 12 | 0.73 |
| Laboratory: Sodium | 20 | 1.21 |
| Laboratory: Creatinine | 10 | 0.60 |
| Laboratory: Glucose | 61 | 3.69 |
| Laboratory: Hematocrit | 13 | 0.79 |
| Laboratory: Potassium | 27 | 1.63 |
| RR syst | 13 | 0.79 |
| RR diast | 13 | 0.79 |
| Heart rate | 2 | 0.12 |
| Oxygen saturation | 29 | 1.75 |
| Fever | 158 | 9.56 |
| Before: Nausea or vomiting | 27 | 1.63 |
| Before: Diaphoresis | 36 | 2.18 |
| Before: Palpitations | 67 | 4.05 |
| Before: Chest pain | 38 | 2.30 |
| Before: Blurred vision | 97 | 5.87 |
| Before: Lightheadedness | 42 | 2.54 |
| Before: Dyspnea | 42 | 2.54 |
| Before: Weakness | 37 | 2.24 |

| | | |
|---|---|---|
| Before: Pain | 37 | 2.24 |
| After: Nausea or vomiting | 23 | 1.39 |
| After: Diaphoresis | 127 | 7.68 |
| After: Palpitations | 44 | 2.66 |
| After: Chest pain | 40 | 2.42 |
| After: Lightheadedness | 146 | 8.83 |
| After: Dyspnea | 40 | 2.42 |
| After: Pain | 43 | 2.60 |
| After: Weakness | 36 | 2.18 |
| After: Weakness | 40 | 2.42 |
| Supine | 13 | 0.79 |
| Sitting | 15 | 0.91 |
| While standing up | 19 | 1.15 |
| Standing | 17 | 1.03 |
| During exercise | 20 | 1.21 |
| Fall | 43 | 2.60 |
| Incontinence | 60 | 3.63 |
| Evidence of infection | 86 | 5.20 |
| Status: Head trauma | 20 | 1.21 |
| Status: Neurologic deficits | 47 | 2.84 |
| Status: Auscultation | 81 | 4.90 |
| Status: Systolic heart murmur | 83 | 5.02 |
| Status: Diastolic heart murmur | 87 | 5.26 |
| Status: Edema | 86 | 5.20 |
| Status: Injury | 45 | 2.72 |

## Supplemental tables

### Supplemental table 1

| Supplemental table 1 – Patients characteristics | All patients | Cardiac | Non cardiac | Unknown | p-value |
|---|---|---|---|---|---|
| Number of patients | 1653 | 252 | 1242 | 159 | |
| Age-years (median [IQR]) | 71.0 [57.0, 80.0] | 77.0 [66.0, 83.2] | 68.0 [55.0, 78.0] | 79.0 [70.5, 84.0] | <0.001 |
| Female - no. (%) | 663 (40) | 88 (35) | 511 (41) | 64 (40) | 0.067 |
| Characteristics of the syncope - no. (%) | | | | | |
| Nausea or vomiting | 486 (30) | 49 (20) | 411 (34) | 26 (17) | <0.001 |
| Sweating | 506 (31) | 48 (19) | 434 (36) | 24 (15) | <0.001 |
| Pallor | 449 (44) | 56 (37) | 363 (47) | 30 (32) | 0.021 |
| Palpitations | 113 (7) | 26 (11) | 81 (7) | 6 (4) | 0.043 |
| Angina | 98 (6) | 24 (10) | 66 (5) | 8 (5) | 0.019 |
| Caused injury | 232 (14) | 38 (16) | 163 (13) | 31 (20) | 0.361 |
| Position of the syncope - no. (%) | | | | | |
| While lying | 43 (3) | 6 (2) | 34 (3) | 3 (2) | 1.000 |
| While sitting | 648 (40) | 86 (35) | 500 (41) | 62 (39) | 0.076 |
| Orthostatic | 203 (12) | 19 (8) | 171 (14) | 13 (8) | 0.007 |
| While standing | 735 (45) | 135 (54) | 521 (42) | 79 (50) | 0.001 |
| Exertion | 141 (9) | 44 (18) | 80 (7) | 17 (11) | <0.001 |
| Risk factors - no. (%) | | | | | |
| Hypertension | 995 (60) | 167 (67) | 707 (57) | 121 (77) | 0.005 |
| Hypercholesterolemia | 686 (43) | 117 (48) | 493 (41) | 76 (51) | 0.046 |
| Diabetes | 245 (15) | 48 (19) | 167 (13) | 30 (19) | 0.024 |
| Smoking | 831 (51) | 117 (47) | 630 (51) | 84 (54) | 0.296 |
| History - no. (%) | | | | | |
| Previous stroke | 136 (8) | 22 (9) | 91 (7) | 23 (14) | 0.432 |
| Chronic heart failure | 121 (7) | 36 (15) | 67 (6) | 18 (12) | <0.001 |

| Supplemental table 1 – Patients characteristics | All patients | Cardiac | Non cardiac | Unknown | p-value |
|---|---|---|---|---|---|
| (NYHA II-IV) | | | | | |
| Arrhythmia | 356 (22) | 102 (41) | 211 (17) | 43 (28) | <0.001 |
| Pacemaker | 75 (5) | 20 (8) | 48 (4) | 7 (4) | 0.008 |
| ICD or CRT | 43 (3) | 17 (7) | 22 (2) | 4 (3) | <0.001 |
| Coronary artery disease | 367 (23) | 86 (35) | 230 (19) | 51 (32) | <0.001 |
| Previous DVT or PE | 116 (7) | 18 (7) | 81 (7) | 17 (11) | 0.678 |
| Previous MI | 217 (13) | 52 (21) | 138 (11) | 27 (17) | <0.001 |
| Chronic medication - no. (%) | | | | | |
| ACEIs/ARBs | 751 (45) | 131 (52) | 530 (43) | 90 (57) | 0.008 |
| Alphablocker | 129 (8) | 21 (8) | 92 (7) | 16 (10) | 0.602 |
| Antiarrhythmics Class I | 64 (4) | 19 (8) | 36 (3) | 9 (6) | 0.001 |
| Aspirin | 501 (30) | 93 (37) | 345 (28) | 63 (40) | 0.005 |
| Beta-blockers | 529 (32) | 108 (43) | 352 (28) | 69 (43) | <0.001 |
| Calcium antagonists | 283 (17) | 48 (19) | 194 (16) | 41 (26) | 0.189 |
| Digitalis | 28 (2) | 12 (5) | 13 (1) | 3 (2) | <0.001 |
| Diuretics | 504 (30) | 109 (43) | 331 (27) | 64 (40) | <0.001 |

IQR = Interquartile Range, DVT=Deep venous thrombosis, PE= Pulmonary embolism, MI= Myocardial infarction, ACEI =Angiotensin converting enzyme inhibitors , ARB= Angiotensin receptor blockers, NYHA = New York Heart Association. P-values are calculated between cardiac and non-cardiac syncope.

Supplemental table 2

| Supplemental table 2 – recruitment centers | Overall |
|---|---|
| Number of patients | 1653 |
| Per center (%) | |
| Basel | 824 (50) |
| Liestal | 88 (5) |
| Lachen | 71 (4) |
| Barcelona del Mar | 83 (5) |
| Nuernberg | 105 (6) |
| Zuerich | 120 (7) |
| Rom | 34 (2) |
| Barcelona Clinic | 139 (8) |
| Houston | 19 (1) |
| Brisbane | 49 (3) |
| Madrid | 1 (0) |
| Christchurch | 120 (7) |
| Per region (%) | |
| Switzerland | 1103 (67) |
| Europe | 361 (22) |
| USA, AUS and NZ | 188 (11) |

Supplemental table 3

| Supp. Table 3– Hospitalization and diagnostics according to ESCJ quintiles | First quintile (ESCJ 0% to ESCJ 10%) | Second quintile (ESCJ 12% to ESCJ 20%) | Third quintile (ESCJ 21% to ESCJ 44%) | Fourth quintile (ESCJ 45% to ESCJ 74%) | Fifth quintile (ESCJ 75% to ESCJ 100%) | P for trend |
|---|---|---|---|---|---|---|
| Number of patients | 591 | 207 | 245 | 295 | 315 | |
| Hospitalized – n (%) | 132 (22) | 86 (42) | 111 (45) | 151 (51) | 222 (70) | <0.001 |
| Echocardiography – n (%) | 104 (18) | 54 (26) | 82 (33) | 129 (44) | 165 (52) | <0.001 |
| Holter ECG – n (%) | 49 (8) | 17 (8) | 50 (20) | 75 (25) | 54 (17) | <0.001 |
| Chest X-ray – n (%) | 188 (32) | 94 (45) | 125 (51) | 173 (59) | 191 (61) | <0.001 |
| Telemetry – n (%) | 39 (7) | 31 (15) | 41 (17) | 78 (26) | 115 (37) | <0.001 |
| Loop recorder – n (%) | 5 (1) | 3 (1) | 4 (2) | 9 (3) | 13 (4) | 0.011 |
| Carotis ultrasonography – n (%) | 22 (4) | 10 (5) | 20 (8) | 31 (11) | 17 (5) | 0.001 |
| Coronary angiography – n (%) | 7 (1) | 1 (0) | 9 (4) | 20 (7) | 43 (14) | <0.001 |
| SPECT – n (%) | 2 (0) | 2 (1) | 4 (2) | 6 (2) | 11 (3) | 0.005 |

ESCJ = Early Standardized Clinical Judgement; SPECT = Single Photon Emission Computer Tomography

Supplemental table 4

| Supp Table 4.A - Variables and levels for the diagnosis of cardiac syncope in the whole cohort | | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | | **Level** | **Estimate** | **Lower 95%-CI** | **Upper 95%-CI** | **p-value** |
| ECG parameters | AV Block | Mobitz Typ II or III° | 13.41 | 1.85 | 284.76 | 0.028 |
| | | I° or Mobitz Type I | 1.63 | 1.06 | 2.49 | 0.025 |
| | Heart rate | Tachycardia (>100bpm) | 5.68 | 2.09 | 16.3 | <0.001 |
| | | Bradycardia (<45bpm) | 5.6 | 2.11 | 14.72 | <0.001 |
| | ST depression | Present | 5.16 | 2.48 | 10.65 | <0.001 |
| | | Present but previously known | 1.6 | 0.35 | 5.84 | 0.505 |
| | Arrhythmia (Ventricular extrasystoles, couplets, triplets, runs, non-sustained VT) | Present | 4.94 | 2.95 | 8.23 | <0.001 |
| | | Present but previously known | 1.08 | 0.24 | 4.11 | 0.915 |
| | Complete bundle branch block: | Present | 2.7 | 1.43 | 5.15 | 0.002 |
| | | Present but previously known | 1.84 | 0.82 | 4.07 | 0.134 |
| | Abnormal rhythm (Atrial fibrillation or flutter, ventricular or atrial ectopy, PM rhythm) | Present | 2.66 | 1.59 | 4.44 | <0.001 |
| | | Present but previously known | 1.48 | 0.8 | 2.69 | 0.202 |
| | Axis: Abnormal (Right, extreme left or extreme right axis) | Present | 0.89 | 0.52 | 1.48 | 0.654 |
| | Long QT≥460 | | 1.47 | 0.98 | 2.18 | 0.058 |
| | QRS (continuous) | | 1 | 0.99 | 1.01 | 0.711 |
| Status | Systolic heart murmur | 4-6/6 | 10.67 | 4.37 | 27.55 | <0.001 |
| | | 2-3/6 | 1.83 | 1.13 | 2.93 | 0.013 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Edema | | 2.16 | 1.3 | 3.52 | 0.002 |
| Situation | During exertion | | 2.56 | 1.57 | 4.11 | <0.001 |
| Comorbidities | Valvular disease | | 1.76 | 1.08 | 2.84 | 0.021 |
| | History of arrhythmia | | 1.47 | 0.97 | 2.2 | 0.064 |
| | Age (continuous) | | 1.01 | 1 | 1.02 | 0.174 |
| Symptoms | Before syncope | Clammy sweat | 0.72 | 0.49 | 1.04 | 0.087 |

**Supp Table 4.B - Variables and levels for the determination of the EICJ in the whole cohort**

| **Variable** | | **Level** | **Estimate** | **Lower 95%-CI** | **Upper 95%-CI** | **p-value** |
|---|---|---|---|---|---|---|
| ECG | AV block | Mobitz Typ II or III° | 42.48 | 27.19 | 57.76 | <0.001 |
| | | I° or Mobitz Type I | 4.57 | 0.53 | 8.61 | 0.027 |
| | Abnormal rhythm (Atrial fibrillation or flutter, ventricular or atrial ectopy, PM rhythm) | Present | 9.91 | 4.69 | 15.13 | <0.001 |
| | Complete bundle branch block | Present | 9.68 | 3.18 | 16.17 | 0.004 |
| | | Present but previously known | 4.04 | -4.25 | 12.33 | 0.34 |
| | Arrhythmia (Ventricular extrasystoles, couplets, triplets, runs, non-sustained VT) | Present | 9.37 | 3.58 | 15.16 | 0.002 |
| | | Present but previously known | 2.26 | -11.6 | 16.11 | 0.75 |
| | Long QT≥460 | | 3.15 | -0.66 | 6.96 | 0.105 |
| | QRS (continuous) | | -0.03 | -0.11 | 0.06 | 0.563 |
| Laboratories | Troponin | Measured: Normal | 10.99 | 6.93 | 15.05 | <0.001 |
| | | Measured: Abnormal (≥respective assay's cut-off) | 10.96 | 7.11 | 14.81 | <0.001 |
| | D-Dimers | Measured: Abnormal (≥0.5mg/L) | 10.48 | 5.17 | 15.79 | <0.001 |
| | | Measured: Normal (<0.5mg/L) | 2.98 | -2.33 | 8.29 | 0.271 |
| | BNP | Measured: Abnormal (≥300pg/mL) | 4.96 | -1.77 | 11.69 | 0.149 |
| | | Measured: Normal (<300pg/mL) | 0.37 | -3.48 | 4.22 | 0.852 |
| Diagnostic tests | Chest Xray | Assessed : Abnormal | 9.53 | 5.37 | 13.7 | <0.001 |
| | | Assessed : Normal | 4.78 | 1.57 | 7.98 | 0.004 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Schellong | Assessed: Pathologic | -1.7 | -6.15 | 2.75 | 0.455 |
| | | Not assessed | 6.73 | 3.57 | 9.88 | <0.001 |
| Symptoms | After syncope | Chest pain | 8.92 | 2.62 | 15.22 | 0.006 |
| | | Other pains | 5.52 | 0.05 | 10.99 | 0.048 |
| | | Abdominal pain | 0.2 | -7.45 | 7.86 | 0.959 |
| | | Pain due to injury | -0.9 | -9.31 | 7.5 | 0.833 |
| | | Headache | -1.69 | -5.62 | 2.23 | 0.399 |
| | | Backache | -5.61 | -13.4 | 2.18 | 0.158 |
| | Before syncope | Nausea | -2.76 | -5.84 | 0.31 | 0.079 |
| | | Clammy sweat | -3.2 | -6.25 | -0.15 | 0.04 |
| Comorbidities | Valvular disease | | 7.82 | 2.86 | 12.77 | 0.002 |
| | History of arrhythmia | | 6.95 | 2.97 | 10.93 | <0.001 |
| | Age | | 0.13 | 0.01 | 0.24 | 0.036 |
| Situation | During exertion | | 7.4 | 2.42 | 12.37 | 0.004 |
| Status | Edema | | 4.8 | -0.56 | 10.16 | 0.08 |
| | Signs of infection | | -9.08 | -13.76 | -4.4 | <0.001 |
| Medications | Statins | | 3.69 | 0.57 | 6.8 | 0.02 |
| | Diuretics | | 2.25 | -1.09 | 5.59 | 0.186 |

AV = atrioventricular, BNP = B-type natriuretic peptide, CI = Confidence interval, EIJC = Early Integrated Clinical Judgement, VT = Ventricular tachycardia, PM = Pacemaker.

Supplemental table 5 – Baseline characteristics of patients correctly and incorrectly identified as low-risk per the ESCJ (<30% risk per ESCJ)

| | Correctly classified as low-risk | Incorrectly classified as low risk | P value |
|---|---|---|---|
| Number of patients | 747 | 21 | |
| Age-years (median [IQR]) | 64.0 [52.0, 76.0] | 77.0 [70.0, 80.0] | 0.001 |
| Female - no. (%) | 327 (44) | 9 (43) | 1.000 |
| **Symptoms** | | | |
| Nausea or vomiting | 281 (38) | 4 (20) | 0.160 |
| Sweating | 282 (38) | 7 (35) | 0.935 |
| Palpitations | 49 (7) | 1 (5) | 1.000 |
| Angina | 34 (5) | 2 (10) | 0.565 |
| **Situation** | | | |
| Supine | 25 (3) | 0 (0) | 0.843 |
| Sitting | 313 (42) | 5 (25) | 0.188 |
| Orthostatic | 105 (14) | 3 (14) | 1.000 |
| Standing | 295 (40) | 12 (60) | 0.118 |
| Exertion | 44 (6) | 1 (5) | 1.000 |
| **Past medical history** | | | |
| Hypertension | 385 (52) | 16 (76) | 0.045 |
| Diabetes | 86 (12) | 4 (19) | 0.480 |
| Previous stroke | 38 (5) | 2 (10) | 0.693 |
| Chronic heart failure (NYHA II-IV) | 30 (4) | 2 (11) | 0.424 |
| Arrhythmia | 82 (11) | 6 (30) | 0.025 |
| Coronary artery disease | 109 (15) | 8 (38) | 0.009 |
| Previous MI | 63 (8) | 7 (33) | <0.001 |
| Previous DVT or PE | 38 (5) | 3 (14) | 0.175 |
| Epilepsy | 20 (3) | 0 (0) | 0.944 |
| Valvular defect | 38 (5) | 3 (16) | 0.133 |
| **Status** | | | |
| Edema | 23 (3) | 4 (21) | 0.001 |
| Signs of infection | 92 (13) | 1 (5) | 0.529 |
| **Medications** | | | |
| Statin | 178 (24) | 8 (38) | 0.212 |
| Diuretics | 162 (22) | 5 (24) | 1.000 |
| Anti-arrhythmics | 16 (2) | 1 (5) | 0.958 |
| Aspirin | 188 (25) | 12 (57) | 0.002 |

| | Correctly classified as low-risk | Incorrectly classified as low risk | P value |
|---|---|---|---|
| Beta-blocker | 178 (24) | 11 (52) | 0.006 |
| **ECG parameters** | | | |
| AV block | | | - |
| None | 667 (89) | 16 (76) | |
| I° or II°I | 80 (11) | 5 (24) | |
| II°II or III° | 0 (0) | 0 (0) | |
| Abnormal rhythm | 35 (5) | 6 (29) | <0.001 |
| Complete bundle branch block | | | 0.752 |
| None | 698 (93) | 19 (90) | |
| New | 32 (4) | 1 (5) | |
| Present, known | 17 (2) | 1 (5) | |
| Arrhythmia | | | 0.001 |
| None | 716 (96) | 17 (81) | |
| New | 26 (3) | 4 (19) | |
| Present, known | 5 (1) | 0 (0) | |
| QT (median [IQR]) | 432.0 [416.0, 451.0] | 442.0 [432.8, 472.0] | 0.012 |
| QRS (median [IQR]) | 92.0 [84.5, 102.0] | 93.0 [90.0, 104.0] | 0.367 |
| **Diagnostics** | | | |
| Schellong | | | 0.664 |
| Normal | 254 (34) | 7 (33) | |
| Pathologic | 122 (16) | 2 (10) | |
| Not conducted | 371 (50) | 12 (57) | |
| Chest xray : Normal | 188 (72) | 7 (58) | 0.470 |
| **Biomarkers** | | | |
| D-Dimer (median [IQR]) | 0.6 [0.3, 1.4] | 1.0 [0.6, 1.6] | 0.136 |
| hs-cTnI (median [IQR]) | 3.3 [2.1, 7.0] | 12.1 [6.8, 39.7] | <0.001 |
| BNP (median [IQR]) | 29.7 [12.8, 67.4] | 148.8 [77.8, 478.4] | <0.001 |

Characteristics of the patients correctly classified as low risk (ESCJ <30% and no cardiac syncope) and incorrectly classified as low risk (ESCJ <30% but diagnosed with a cardiac syncope).

## Supplemental figures

### Supplemental figure 1

# BASEL IX Syncope study

**Study center:** **ID:** _____ Patient label

Date of entry ___ . ___ . _____ (dd . mm . yyyy) Time of entry _____ : _____ (time of first contact with medical staff) Referred by _____

Study inclusion _____ : _____ (hh : mm) GP _____

**1. Syncope** (if the duration of syncope is unclear, check either seconds or minutes)

Date ___ . ___ . _____ (dd . mm . yyyy) Time _____ : _____ (hh : mm) Syncope witnessed ☐ yes ☐ no

Unconsciousness uncertain ☐ Duration _____ : _____ (mm : ss) Same witness present ☐ yes ☐ no

| **2. Situation** | yes | no | n.a. |
|---|---|---|---|
| Getting up | ☐ | ☐ | ☐ |
| standing | ☐ | ☐ | ☐ |
| During physical effort | ☐ | ☐ | ☐ |
| Overhead work | ☐ | ☐ | ☐ |
| While sat down | ☐ | ☐ | ☐ |
| while in supine position | ☐ | ☐ | ☐ |
| Fall | ☐ | ☐ | ☐ |

| **4. During syncope** | yes | no | n.a. |
|---|---|---|---|
| Myoclonia | ☐ | ☐ | ☐ |
| Cyanosis | ☐ | ☐ | ☐ |
| Tongue bite | ☐ | ☐ | ☐ |
| Loss of urine/stool | ☐ | ☐ | ☐ |

**5. On awakening** awake/orientated ☐ tired ☐ desorientated ☐

| **3. Prodromal symptomes** | yes | no | n.a. |
|---|---|---|---|
| Sweating | ☐ | ☐ | ☐ |
| Nausea/vomiting | ☐ | ☐ | ☐ |
| "visual black out" | ☐ | ☐ | ☐ |
| Paleness | ☐ | ☐ | ☐ |
| Dizziness/Vertigo | ☐ | ☐ | ☐ |
| Palpitations | ☐ | ☐ | ☐ |
| Angina Pectoris | ☐ | ☐ | ☐ |

Dyspnea **prior** 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
(0=none, 1=slight, 2 =moderate, 3=strong, 4=very strong)

General weakness 0 ☐ 1 ☐ 2 ☐
(0=None, 1=slight, 2=marked)

Pain **prior** none ☐ Head ☐ Chest ☐ Back ☐ Abdo. ☐ other ☐

| **6. After syncope** | yes | no | n.a. |
|---|---|---|---|
| Sweating | ☐ | ☐ | ☐ |
| Nausea/vomiting | ☐ | ☐ | ☐ |
| Dizziness/Vertigo | ☐ | ☐ | ☐ |
| Palpitations | ☐ | ☐ | ☐ |
| Angina Pectoris | ☐ | ☐ | ☐ |

Dyspnea **after** 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
(0=none, 1=slight, 2 =moderate, 3=strong, 4=very strong)

General weakness 0 ☐ 1 ☐ 2 ☐
(0=None, 1=slight, 2=marked)

Pain **after** none ☐ Head ☐ Chest ☐ Back ☐ Abdo. ☐ other ☐

Memo

**Please do NOT FORGET**

**7. Likelyhood of cardiac syncope,** done by treating physician in E.D. after history, examination, ECG and lab results

How likely has this syncope an underlying cardiac cause?
CARE: cardiac/cardiovascular = e.g. ACS, Stroke, pulmonary embolism, aortic dissection, rhythmogenic etc.

**0 ----- 10 ----- 20 ----- 30 ----- 40 ----- 50 ----- 60 ----- 70 ----- 80 ----- 90 ----- 100 %**

Treating doctor's hypothesis: _____

**8. Medical history** yes no n.a.

**History of syncope** ☐ ☐ ☐ How many? ☐

Last syncope? (prior to index) _____

Known CAD ☐ ☐ ☐ If "yes", please fill next row:

Status post MI ☐ St.p. PCI ☐ St.p. CABG ☐ no MI or revascularisation to date ☐

| | yes | no | n.a. |
|---|---|---|---|
| Hypertension | ☐ | ☐ | ☐ |
| Hypercholesterolemia | ☐ | ☐ | ☐ |
| Diabetes Mellitus | ☐ | ☐ | ☐ |
| Smoker (active or former) | ☐ | ☐ | ☐ |
| If "yes" active _____ PY former: _____ PY | | | |
| Known cardiac arrhythmia | ☐ | ☐ | ☐ |
| Pacemaker | ☐ | ☐ | ☐ |
| ICD | ☐ | ☐ | ☐ |
| Chronic heart failure | ☐ | ☐ | ☐ |
| If "yes", NYHA class _____ | | | |
| Known valvular heart disease | ☐ | ☐ | ☐ |

| | yes | no | n.a. |
|---|---|---|---|
| PAOD | ☐ | ☐ | ☐ |
| St.p. DVT/PE | ☐ | ☐ | ☐ |
| St.p. intracranial bleeding | ☐ | ☐ | ☐ |
| St.p. Stroke | ☐ | ☐ | ☐ |
| Known epilepsy | ☐ | ☐ | ☐ |
| GI bleeding (within 7 days) | ☐ | ☐ | ☐ |

**9. Family history** yes no n.a.

| | | | |
|---|---|---|---|
| Sudden cardiac death | ☐ | ☐ | ☐ |
| CAD | ☐ | ☐ | ☐ |
| Stroke | ☐ | ☐ | ☐ |

(History of CAD: father/brother <55, mother/sister <65)

Alcohol consumption ☐ never ☐ occasional ☐ daily

Other drugs, e.g. Cannabis, Opiates ☐ ☐ ☐

If "yes", which? _____

**10. Vital signs**

Height _____ cm Weight _____ kg BP _____ / _____ mmHg Heart rate _____ / min.

Temperature _____ °C $O_2$ Saturation _____ % at _____ l $O_2$ / min. Breathing rate _____ / min.

**11. GCS** _____ Use first score documented in E.D.

Vigilance (during questionnaire) ☐ awake/orientated ☐ tired ☐ desorientated

**12. Clinical tests** According to treating physician's exam if possible

| | yes | no | n.a. |
|---|---|---|---|
| Face/head injury | ☐ | ☐ | ☐ |
| New neurologic deficit | ☐ | ☐ | ☐ |
| Carotid bruit | right ☐ left ☐ | ☐ | ☐ |
| Systolic murmurs | ___ / 6 | ☐ | ☐ |
| Diastolic murmurs | ___ / 6 | ☐ | ☐ |
| Pulmonal basal crackles | right ☐ left ☐ | ☐ | ☐ |
| Rectal bleeding (only if examined) | ☐ | ☐ | ☐ |
| Other signs of bleeding | ☐ | ☐ | ☐ |
| Peripheral edema | ☐ | ☐ | ☐ |
| other injuries | ☐ | ☐ | ☐ |
| If "yes", location of injury | _____ | | |
| Signs of infection | ☐ | ☐ | ☐ |
| If "yes", probable focus of infection | _____ | | |

**13. Ethnicity:** Caucasian ☐ African ☐ Asian ☐ other ☐

## BASEL IX Syncope study

**Studycenter** **ID:** _____ Patient label

| **14. Further examinations at E.D.** | normal | pathologic | not done | n.a. |
|---|---|---|---|---|
| Blood pressure difference | ☐ | ☐ | ☐ | ☐ |
| Lying to standing test (please fill below) | ☐ | ☐ | ☐ | ☐ |
| Cranial CT | ☐ | ☐ | ☐ | ☐ |
| Other _____ | ☐ | ☐ | ☐ | ☐ |

**Examinations scheduled by E.D.**

_____

| **Lying-to-standing test** | yes | no | n.a. | | BP (mmHg) | HR / min. |
|---|---|---|---|---|---|---|
| Clinical symptoms | ☐ | ☐ | ☐ | supine position | _____ / _____ | _____ |
| If "yes", please specify: | | | | standing positions | _____ / _____ | _____ |
| | | | | after 3 min standing | _____ / _____ | _____ |
| | | | | afer 5 min standing | _____ / _____ | _____ |

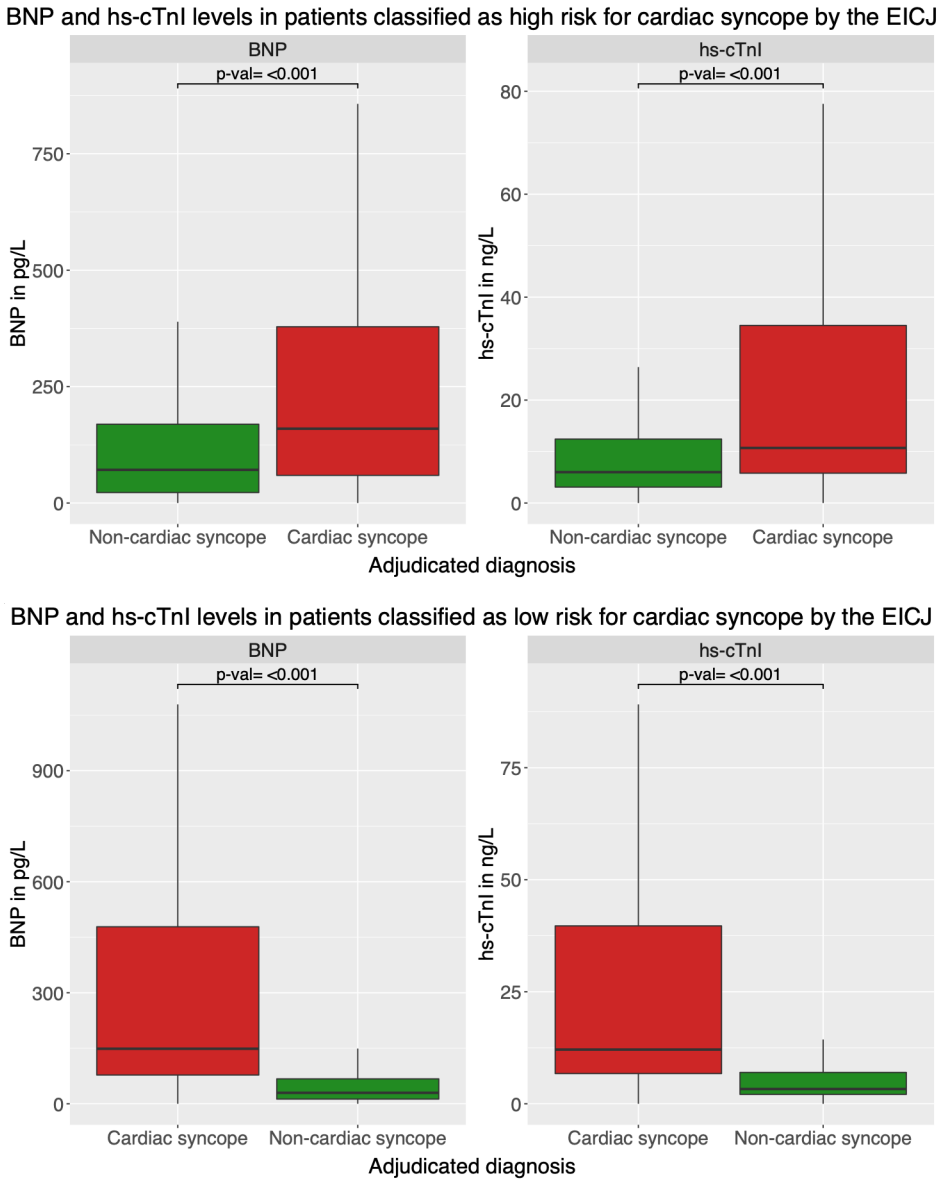
**15. Premedication** **none** ☐

**MEMO** please list all medication, if space does not suffice, use backpage.



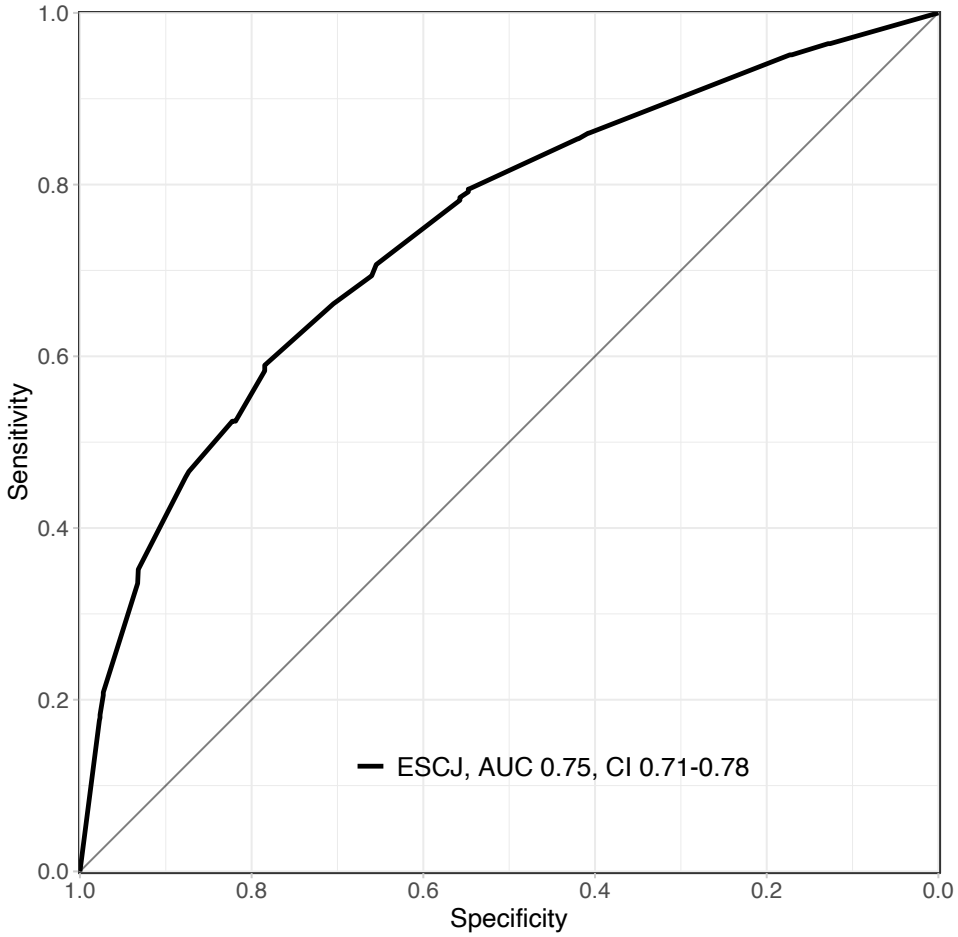
Supplemental figure 1 – CRF used in the study and available to the clinicians before the collection of the ESCJ.

## Supplemental figure 2




Boxplots representing the BNP and hs-cTnI concentrations according to whether or not patients classified as **low- (ESCJ <30%)** or **high-risk (ESCJ >70%)** by the ED physician were correctly or incorrectly classified. Boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test.

## Supplemental figure 3




Performance of the ESCJ for the prognosis of patients presenting to the ED with a syncope. The endpoint is MACE at 1 year (Death, reanimation, life-threatening arrhythmia, implantation of a pacemaker or implantable cardioverter defibrillator (ICD), acute myocardial infarction, stroke/transient ischemic attack (TIA), intracranial bleeding, valvular surgery and pulmonary embolism)

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